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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/469,611	Jun 06, 1995	[illegible]	[illegible]

EXAMINER

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ART UNIT	PAPER NUMBER
[illegible]	11

DATE MAILED: 10/31/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7 July 1997.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 21-40 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 21-30, 34-39 is/are allowed.

☒ Claim(s) 31-33 and 40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply + marked-up copy of Raw Sequence Listing

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1998-410-238/40050

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1646.

Continued Prosecution Application

1. The request filed on 11 March 1998 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/469,641 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 57, 63 and 69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are directed to RNA. However, the claims from which they depend are DNA (SEQ ID NO:1 is DNA) and the specification does not teach how to make RNA with thymine instead of uracil.

4. Claim 73 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling methods of making a polypeptide by expressing the DNA which encodes the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for methods of making a polypeptide by expressing polynucleotides having 95% identity to polynucleotides which encode a polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claim (73) ultimately depend on claim 41. Claim 41 is directed to polynucleotides which have at least 95% identity to (a, b) a polynucleotide encoding a polypeptide of SEQ ID NO:2, (c) a polynucleotide encoding a polypeptide in an ATCC deposit, (d) the complement of a polynucleotide encoding a polypeptide, and (e) a polynucleotide which hybridizes to (a-d). First, the polynucleotide sequence of (a-e) include degenerate sequences. A polynucleotide having 95% identity to a degenerate sequence encoding a polypeptide would not necessarily encode the protein anymore. Claims to polynucleotides having a percent identity are typically designed as probe claims or for obtaining claims to allelic variants of the naturally occurring DNA. However, as the current claims are drafted, the claimed polynucleotides may bear no resemblance to the naturally occurring polynucleotide encoding the polypeptide. In addition, the polynucleotide of (e) need not even encode a protein since it only needs to hybridize to a sequence that encodes (or is the complement thereof). In Ex parte Forman, 230 USPQ 546 (Bd. Pat. Appls, and Interf. 1986), the Board considered the issue of enablement in molecular

biology. The Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation:

(a) quantity of experimentation necessary
(b) amount of direction or guidance presented
(c) presence or absence of working examples
(d) nature of the invention
(e) state of the prior art
(f) relative skill of those in the art
(g) predictability or unpredictability of the art and
(h) breadth of the claims.

In the instant case, the claims broadly encompass any polynucleotide having at least 95% identity to a polynucleotide encoding a polypeptide (comprising a specific amino acid sequence) or having at least 95% identity to a polynucleotide which hybridizes to a polynucleotide which encodes a polypeptide. It would require undue experimentation by one of ordinary skill in the art to determine which of the multitude of polynucleotide's encompassed by the instant claims that meet the structural limitations (being 95% identical to a polynucleotide) would also meet the functional limitations of the claims (encoding a polypeptide). The specification provides a single example of a polynucleotide which encodes a polypeptide (SEQ ID NO:1) but fails to describe even a single other working example. The instant claims encompass variants, analogs, and derivatives, yet the specification provides no guidance or examples as how the polynucleotide could be modified and still encode a polypeptide with the activity of the polypeptide of SEQ ID NO:2. The nature of the invention is novel in that the polynucleotide and polynucleotide of SEQ ID NO:1 and encoding the amino acid sequence of SEQ ID NO:2 are not known in the prior art, therefore, no guidance

can be obtained from the prior art. The skill in the art may be high, but it is well known and established that the art of mutating proteins and retaining biological activity is unpredictable. Therefore, the experimentation required to practice the claimed invention would be considered undue, absent evidence to the contrary.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 41-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites "a polynucleotide at least 95% identical to". However, the use of % identity is indefinite without a recitation of an algorithm for calculating this identity. In determining identity, there are a number of variables which must be selected and are necessary for the calculation of identity. Based on the selection of values for these variables, the % identity can vary immensely. For example, consider two sequences: acgtac and acac. These can be compared in any of four ways.

acgtac	4/6=67%	acgtac	2/6=33%
|| ||		||	
ac--ac	4/4=100%	acac	2/4=50%

Depending how gaps and lengths are calculated, the percent identity between these two simple sequences can vary from 100% to 33%. In addition, the reference George et al. is provided with this Office action which demonstrates the numerous types of algorithms which can be used to calculate identity and how selection of values for the variables will influence this calculation (i.e. gaps, lengths, etc.). As taught by George et al., "[t]he results of the analysis are entirely dependent on the choice of scoring rules" (see page 130). Therefore, the recitation of %identity without the provision of a specific algorithm in the instant specification as how this identity is to be calculated is indefinite and the metes and bounds of the claims cannot be determined.

7. Claims 41, 50, 51 encompass an isolated polynucleotide which hybridizes under stringent conditions. There are several factors which affect the hybridization of nucleic acids and there are a multitude of conditions which may or may not be considered stringent because stringency is a relative condition. Without some sort of guidance or definition of what this term is meant to encompass, the metes and bounds of the instant claim cannot be determined, thereby making the claim indefinite. If the claim incorporated those conditions which are considered stringent, wherein basis for the conditions are found in the instant specification as filed, this ground of rejection could be overcome. (It should be noted that prior art may be applied to an amended at that time based on the hybridization conditions and the amendment would be considered as necessitating any new grounds of rejection based on the stringency conditions.)

8. Claim 41 is also indefinite for the recitation "comprising a polynucleotide at least 95% identical to a member" because it is not clear what property is intended to be 95% identical. If

mere physical structure is intended, than any polynucleotide with a nucleotide backbone may suffice. If Applicant intends that the sequence of the polynucleotide be 95% identical to a polynucleotide sequence, then this should be reflected in the claim. (Note: the claim is being interpreted as comprising a polynucleotide sequence which is at least 95% identical to a polynucleotide sequence ...".)

9. Claim 50 is also indefinite because of the recitation of "having a nucleotide sequence identical to a nucleotide sequence in (a), (b), (c), or (d)". It is indefinite because the sequences of (a) and (b) contain comprising language. It is not clear what additional amino acids are included in (a) and (b), therefore the metes and bounds of what would be "identical" cannot be determined.

10. Claim 73 recites the limitation "to produce the polypeptide". This claim ultimately depends from claim 41, for which there is insufficient antecedent basis for the limitation "the polypeptide". The polynucleotides of claim 41 are at least 95% identical to polynucleotides which encode a polypeptide; there is nothing in claim 41 which requires the isolated polynucleotides to encode a protein. Therefore, claim 73 is indefinite and unclear.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 51-52 and 54-56, 58, 60-62, 64, 66-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez et al. (Proc. Natl. Acad. Sci. USA 82: 7666-7670, 1985).

Gonzalez et al. disclose an isolated polynucleotide which comprises at least 30 contiguous nucleotides of SEQ ID NO:1 of the instant application (see Figure 3 of Gonzalez et al.). Nucleotides 3923 to 3958 of Gonzalez et al. are identical to nucleotides 7 to 42 of SEQ ID NO:1. This polynucleotide of Gonzalez et al. is DNA (see Figure 3) and is provided in single stranded (see Figure 3) and double stranded (see Methods at page 7666, column 2 in that the gene was cloned, which requires double stranded DNA) form. The coding strand of DNA is described in Figure 3, but Gonzalez et al. also had possession of the complementary strand because the entire DNA was in possession (see Methods). This complementary strand would also necessarily hybridize under stringent conditions to the coding strand. Therefore, Gonzalez et al. anticipates the claims.

13. Claims 51-56, 58-62, 64-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Eriksson et al. (U.S. Pat. No. 5,607,918).

Eriksson et al. disclose an isolated polynucleotide which comprises at least 50 contiguous nucleotides of SEQ ID NO:1 of the instant application (see SEQ ID NO:10, Figure 10 of Eriksson et al.). This polynucleotide of Eriksson et al. is DNA (see Figure 10) and is provided in single stranded (see Figure 10) and double stranded (see Example 4 at column 9 beginning line 38

which demonstrates the cloning of human VEGF-B_{166} which corresponds to SEQ ID NO:10; the cloned DNA would necessarily be double stranded) form. The coding strand of DNA is described in Figure 10, but Eriksson et al. also had possession of the complementary strand because the entire DNA was in possession (see Example 4). This complementary strand would also necessarily hybridize under stringent conditions to the coding strand. Therefore, Eriksson et al. anticipates the claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 57, 63, and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al.

The disclosure of Gonzalez et al. is as described above. Gonzalez et al. do not expressly teach polynucleotides which are RNA. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to create RNA probes of the polynucleotide of Gonzalez et al. in order to detect mRNA in various tissues. It was routine at the time of the instant invention to make synthetic RNA probes based on DNA molecules, therefore, one of ordinary skill in the art would have a reasonable expectation of success as well as sufficient motivation.

16. Claims 57, 63, and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksson et al.

The disclosure of Eriksson et al. is as described above. Eriksson et al. do not expressly teach polynucleotides which are RNA. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to create RNA probes of the polynucleotide of Eriksson et al. in order to detect mRNA in various tissues. It was routine at the time of the instant invention to make synthetic RNA probes based on DNA molecules, therefore, one of ordinary skill in the art would have a reasonable expectation of success as well as sufficient motivation.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Sylvester et al. Gene 84: 193-196, 1989.
Kern et al. Science 252: 1708-1711, 1991.

Sylvester et al. and Kern et al. both teach DNA which comprises at least 30 contiguous nucleotides of SEQ ID NO:1. These references are not cited in the rejections above because they would be somewhat duplicative of the instant rejections under 102 and 103 for claims 51-52 and 54-56-58, 60-64, 66-69. However, if an amendment to the claims eliminates Gonzalez et al. as prior art, Sylvester et al. and Kern et al. may be relied upon as prior art.

18. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
May 18, 1998

JOHN ULM
PRIMARY EXAMINER
GROUP 1800